REMARKS

All references to the locations in the application contained in this Response will be based on the application as published May 12, 2005.

Rejection under 35 USC 112

At pages 2-4 of the Office Action, the Examiner has rejected the claims under 35 USC 112 holding that "the length limitation finds support in the specification, the limitation that the strands are non-linked does not." The general basis of this rejection is that the presently pending claims that require the isolated dsRNA to be 15-21 base pairs in length and consisting of two separate non-linked strands is not supported by the priority documents and hence constitute new matter.

Applicants respectfully traverse this rejection based on the following remarks. Applicants respectfully assert that the Inventors, as provided in the PCT priority document, contemplated a length range of 15-49 base pairs for the dsRNA in which the dsRNA consisted of two separate strands which could additionally contain a chemical linker. In addition, Applicants provided a working example of this invention using a 21 base pair long dsRNA in which the two strands were linked. Using accepted practice, Applicants have presented claims with the recited length range of 15-21 base pairs (using the lower element of the range and an internal example as the upper bound) but which does not contain a required linker function.

It appears that the Examiner agrees that the application discloses the use of dsRNA 15-49 base pairs long [0014].

The point of disagreement states at [0018] where it is disclosed that "the ends of the dsRNA can be modified to counteract degradation in the cell or dissociation into the single strands" [Emphasis added]. Applicants assert that since the terms used are "ends" and not the singular "end" and "single strands" not the singular "single strand" that it is clear that the inventors contemplated and disclosed that two single strand RNAs are used to form the dsRNAs of the invention and that these separate single strands can optionally be further modified with one or more linkers to make the separate strands linked.

From these passages, as well as others in the application, it is clear that the inventors conceived of a range of dsRNA molecules (15-49 base pairs) that could, as an additional feature, contain one or more chemical linkers, but that such linkers did not always need to be present.

An Example that is used to support the upper range limit of 21 in the pending claims uses linked strands. This does not limit the totality of the patent application's disclosure. Nowhere does it say that 15-21 base pairs require a linker while dsRNAs with more base pairs do not. The only statement the Examiner contends "implies the inventors believed that stabilization of the shorter dsRNA is required" was a conclusion about a positive experiment. This however does not limit the totality of the disclosed invention, linked and non linked strands, 15-49 base pairs with a specific example of 21 base pairs allowing Applicants to claim 15-21 base pairs as a claim range (In re Wertheim).

The Examiner clearly recognizes that dsRNA of 15-21 base pairs made of separate non-linked strands work in the RNAi process as evidenced by the cited Zhang (Cell) reference. Zhang simply confirms and supports Applicants' invention.

Rejections Under 35 USC 102

At page 4 of the Office Action, the Examiner has rejected the claims under 35 USC 102(b) as being anticipated by Fosnaugh. Applicants respectfully traverse this rejection based on the following remarks.

The basis of the Examiner's rejection is that the present claims are not supported by the PCT priority document and are only afforded the date they were presented in the present application. As such, the Examiner has cited a reference published after the PCT priority application but before the date of the instant application.

As discussed extensively above, the presently pending claims are supported by the PCT priority application and therefore Fosnaugh is not available as prior art. Accordingly, this rejection may be properly withdrawn.

At page 5 of the office Action, the Examiner has rejected claims 4 and 6-9 as being anticipated by Crooke.

Applicants respectfully traverse this rejection based on the following remarks.

Crooke was investigating a putative dsRNAase in cells using what was called an "artificial substrate" (Table 1) that would mimic the association of a single strand RNA with an RNA target. To this end, Crooke synthesized dsRNA that would mimic the binding of a single stranded RNA cleavage agent with a target RNA sequence and then looked at the resultant product after incubation with various RNAases. The Examiner contends that these synthetic substrates meet all the limitations of the claims and would be expected to function as required by the claims.

Applicants respectfully assert that this is not the case and one would not expect the synthetic substrates provided in Crooke would function in an RNAi process. Specifically, as will be outlined below, the RNAi process can tolerate some modifications to the dsRNA but that significant modification can either be toxic to a cell or lead to inactive molecules. The references discussed below will demonstrate that dsRNAs that are fully substituted with phosphorothioate linkages are toxic to a cell and that dsRNAs with extensive 2'OMe modifications to the antisense strand would be inactive, particularly if the 5' end includes more than one 2'OMe modification. As such, the 4 dsRNAs disclosed in Crooke, which all contain at least an antisense strand having 4 (Ha-ras targeted) or 6 (C-raf target) 2'OMe at the 5' and 3' ends and near complete PS linkages in both the antisense and sense strands would be predicted as not meeting the limitation of the claims of "specifically inhibits the expression of said mammalian target gene" since they would be predicted as being inactive.

a) dsRNAs of Crooke. In Table 1, 4 highly modified dsRNAs are disclosed and are described at column 50, line 51-60:

"The 'sense' strand was an oligoribonucleotide having phosphodiester linkages in an eight-base gap with flanks having either (a) residues with phosphorothioate linkages or (b) 2'-methoxynucleosides with phosphorothioate linkages. The 'antisense' strand in both substrates

contained 2'-methoxy phosphorothioate wings on either side of an eight-base ribonucleotide gap having either phosphodiester or phosphorothioate linkages".

In summary, the 17mer dsRNA of Crooke that have sequence complementarity to Ha-ras would therefore have an antisense with 5' and 3' ends with a total of 9 2'OMe bases split between the ends and will additionally have either 9 or 16 PS linkages, paired with a sense strand that has 9 PS linkages. The 20mer dsRNA have sequence complementarity to C-raf would have and antisense with 5' and 3' ends with a total of 12 2'OMe bases split between the ends and will additionally have either 12 or 19 PS linkages, paired with a sense strand that has 12 PS linkages.

b) Amarzguioui et al (NAR 31:589-595 (2003) (Exhibit A). At the bottom of column 2, page 589, Amarzguioui states that "Extensive use of phosphorothioate modifications result in cytotoxicity". At page 591, Column 1, it is stated that "It has been reported that siRNA with a general 2'-O-methylation in either strand have no activity," and at Column 2 "Allylated siRNAs were not tested in this experiment, since they showed reduced effectivity even with only one substituent in the 5' end," and later in the same column, "The most extensively phosphorothioate siRNA proved to be cytotoxic . . ."

From these passages, it is clear that the extensive phosphorothioate modification in modified dsRNAs of Crooke would be predicted as being cytotoxic and that all agents would be inactive in the RNAi process as well since they contained extensive 2'OMe modifications in the antisense strand, particularly the 5'end.

c) Kraynack and Baker (RNA 12:163-176 (2006) (Exhibit B). Unlike previous reports, Kraynack did find one of four dsRNAs with complete 2'OMe sense strands still retained activity (page 166, bottom of column 1). However, consistent with all previous reports, "duplexes containing either a PO-2'OMe antisense strand . . . or a PS-2'OMe antisense strand . . . were inactive and failed to reduce PTEN mRNA." Sentence spanning column 1-2 page 167.

As above, Kraynack would not predict that the modified 2'OMe dsRNAs of Crooke would be active in RNAi process.

Since there is significant teaching in the art that the agents of Crooke would not function as required by the claims, this rejection may be withdrawn.

At page 5 of the Office Action, The Examiner has rejected claims 4-6 and 8 under 35 USC 102(e) as being anticipated by Fire as evidenced by Zhang. The Examiner has raised this as an inherency rejection holding that "the long dsRNA disclosed in Fire et al are necessarily cleaved into such duplexes" (referring to the 15-21 length limitation in the present claims).

Applicants respectfully traverse this rejection based on the following remarks.

Fire teaches the use of dsRNA with a length of identical nucleotide sequence to the target mRNA that is at least longer than 25nt (Column 8, line 4). Nowhere within Fire is there a teaching or a statement that can be read as teaching an "isolated" dsRNA of 15-21 base pairs as claimed or something that would inherently produce such an isolated molecule. If Fire teaches any isolated dsRNA, it is clearly longer that the claimed range and any action of DICER that occurs in Fire happens within a cell to non-isolated molecules.

Zhang does not cure this deficiency. Zhang shows that within a cell, Dicer cleaves longer dsRNA, such as those of Fire, into short ~20bp fragments. Nowhere in Fire is there a showing that the longer dsRNAs are combined with Dicer to yield isolated 15-21 bp dsRNA. If Dicer cleaves the long dsRNA of Fire, it happens within a cell and would therefore not be provided as an isolated molecule. As such, there cannot be inherent anticipation as stated by the Examiner.

SUMMARY

Applicants have provided arguments to address each of the outstanding rejections of the claims. It is believed that the rejections have been addressed and that the application is in condition for allowance. It is requested that the Examiner contact Applicants undersigned representative if the Examiner believes that a telephonic interview would expedite this case.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States.

No fee is believed due. Please apply any charges or credits to deposit account 06-1050, referencing attorney docket number 14174-105US5.

Respectfully submitted,

Date: 5/24/2006

Robert Millman (617) 551-8331 (direct)
Reg. No. 36,217

Direct all correspondence to:
PTO Customer Number: **26161**
Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906